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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/129,758 | 08/05/1998 | RAINER WALDMANN | 1099-00 | 5113 |

35811 7590 11/17/2003

IP DEPARTMENT OF PIPER RUDNICK LLP
3400 TWO LOGAN SQUARE
18TH AND ARCH STREETS
PHILADELPHIA, PA 19103

| EXAMINER | |
|---|---|
| BASI, NIRMAL SINGH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1646 | 29 |

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/129,758 | WALDMANN ET AL. | |
| | Examiner | Art Unit | |
| | Basi N Bass | 1646 | |

*-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *14 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *1,11-13,15,17-23 and 26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,11-13,15,17-23 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/14/03 has been entered.

2. Amendment filed 8/13/03 has been entered (paper number 25. Claims 1, 11-13, 15, 17-23, 26-29 are pending.

**Claim Rejection, 35 U.S.C. 112**

3. Amended claims 1, 11-13, 15, 17-23 and 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Amended claims 1 and 28 are indefinite because it is not clear what is a "functionally equivalent derivative" so as to allow the metes and bounds of the claim to be determined. Applicant argues the "functionally equivalent derivatives" will have about 67% homology to those nucleic acid and protein defined within the specification and support for the inclusion of this limitation can be seen on page 2, lines 21-23 of the specification which show that the MDEG channel exhibits 67% homology to the ASIC channel. Applicant's arguments have been fully considered but not found persuasive.

The specification does not provide a clear definition of the term "functionally equivalent derivative". The specification, on page 2, lines 21-24 discloses, "The MDEG channel is a structural relative of ASIC channel, the amino acid sequence of which exhibits about 67% homology with the ionic channel MDEG. However, the electrophysiological properties of these two channels are different because they are not activated by the same pH changes". Therefore, based on the specification there is no disclosure of the equivalent function encompassed by the derivatives of at lest 67% homology to SEQ ID NO:2, 4, or 8. On the contrary to Applicants arguments the functions disclosed are not equivalent. Although the specification provides examples of "functionally equivalent derivative", it does not provide a clear definition of the term so as to allow the metes and bounds of the claim to be determined. It is not clear what "functionally equivalent derivative" includes and excludes.

Claim 22 recites the limitation "said cells" in line 4. There is insufficient antecedent basis for this limitation in the claim. Further claim 22 is indefinite because it is not clear if the ASIC channel, in lines 3-4 of the claim, is the same as that in line 5. It is not clear if two populations of cells are contacted with substances to be tested or only one. Lines 3-4 of the claim recite, "measuring the current of said mammalian neuronal cationic ASIC channel prior to contacting said substance with said cells". Line 5 of the claim recites, "contacting variable quantities of a substance to be tested with the cell according to claim 21". Further, the method steps do not achieve the goal of screening a substance capable of modulating activity of mammalian neuronal cationic ASIC channels as stated in the preamble. The measured change in the current may be

result of the modulation of a channel protein which is completely different to the ASIC channel protein contained in the cells according to claim 21. Further, lines 9 and 10 of the claim are a comparison, therefore the "then" on line 9 of the claim should be amended to "than" to be grammatically correct.

Claim 28 recites the limitation "said cells" in line 4. There is insufficient antecedent basis for this limitation in the claim. Further claim 22 is indefinite because it is not clear if the ASIC channel, in lines 3-4 of the claim, is the same as that in line 5. It is not clear if two populations of cells are contacted with substances to be tested or only one. Lines 3-4 of the claim recite, "measuring the current of said mammalian neuronal cationic ASIC channel prior to contacting said substance with said cells". Line 5 of the claim recites, "contacting variable quantities of a substance to be tested with the cell according to claim 27". Further, the method steps do not achieve the goal of screening a substance capable of modulating activity of mammalian neuronal cationic ASIC channels as stated in the preamble. The measured change in the current may be result of the modulation of a channel protein which is completely different to the ASIC channel protein contained in the cells according to claim 27. Further, lines 9 and 10 of the claim are a comparison, therefore the "then" on line 9 of the claim should be amended to "than" to be grammatically correct.

Claims 11-13, 15, 17-21, 23, 26-27 and 29 are rejected for depending upon an indefinite base (or intermediate) claim and fail to resolve the issues raised above.

4. Claims 12-13, 15, 17, 20, 23, and 29 remain rejected, for reasons of record in paper number 23 (2/11/03), under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Amended 1, 11, 18, 19, 21, 22, 26, 27 and 28 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. The amendment of the claims has not resulted in a change in the rejection of record for claims 1, 11, 18, 19, 21, 22, 26, 27 and 28. The rejection under 35 U.S.C. 101 (of record in paper number 23, 2/11/03), of the claims present in the application prior to is instant amendment, is applied to amended claims 1, 11, 18, 19, 21, 22, 26, 27 and 28

Applicants arguments pertaining to the rejection of claims 1-3, 5 11-13, 15 and 17-24 and 26-29 under 35 U.S.C. 101 and 112, first paragraph are summarized below Applicant argues:

a) Identification of proton activated ASIC channels in the sensory neurons and in the neurons of the central nervous system illustrates a well-established utility thanks to their role in the mediation of pain caused by acids. FIG. 8 discloses said channel mRNA is well-expressed by the small neurons of the dorsal root ganglion that behave as nociceptors.

b) Applicants have identified a new cationic channel, which is the first member of a group of cationic channels belonging to the family of amiloride-sensitive degenerine sodium channels. This complex family of ion channels demonstrates varied physiological roles and as a result of characterization of said family and functional

properties thereof an additional member of this family inherently possesses a functional well-established utility.

c) Disclosure of a compound that is similar to a compound having a known activity could be deemed to imply that the novel compound has a related specific activity.

d) Applicants have identified a particular compound, namely a protein contained within mammals, which are altered by any of a number of drugs including, for example, amiloride (a drug that blocks sodium/proton antiport and has been used clinically as a potassium sparing diuretic). Consequently, the Applicants submit that the identification of channels, which are regulated by this drug provide a demonstrated and well-established utility of pharmacological consequence.

e) ASIC protein channels are directly affected by neurological compounds, such as amiloride. Claimed channel is sensitive to acid, and protons. It is well-known in the art that the stimulation of sensory neurons by acids accompanies numerous painful inflammatory reactions. Consequently regulation of these channels and their sensitivity to acids and their role in mechanisms to relieve pain associated with acidity relates to the transmission and treatment of pain.

f) gene therapy could be used in the treatment of individuals who lack a functional ASIC gene.

Applicants arguments have been fully considered but not found persuasive for the reasons given below:

The protein gated channel of instant invention belongs to a complex family of ion channels with varied properties and functions (discussed in previous office Action,

paper number 23 (2/11/03). The observation that claimed invention is an amiloride-sensitive degenerine sodium channel and the disclosure of certain biophysical properties does not provide support for either a specific and substantial asserted utility or a well-established utility. The amiloride sensitivity or biophysical properties do not establish the specific and substantial asserted utility or a well-established utility for the claimed invention. The specification discloses, pages 2 and 3, the family of structural relatives of ASIC channels (also designated as MDEG) have different electrophysiological properties and that no normal physiological function of said MDEG was known until the demonstration of its activation by protons (also see page 17, lines 13-16). Also disclosed, page 5, inactivation and kinetics and the ionic selectivity of the channel formed after co-expression of different MDEG are different than those if only one channel is expressed. The specification, page 5, lines 8-9 states, when referring to claimed invention, "this property is very similar to that of the proton-activated cationic channel which is implicated in the prolonged sensation of pain caused by acidosis. It is very probable that DRASIC and MDEG2 are part of this channel". The claimed ion channel is speculated to be similar to the family of proton-activated ion channels, but there is no disclosure in the specification that instant invention is useful for screening substances capable of modulating the perception of acidity regarding both noiception and taste transduction, said substances being further useful in the fabrication of drugs intended for the treatment or prevention of pathologies entailing the painful perception of acidity which interferes in inflammatory diseases. All members of the ASIC family do not have the same electrophysiological properties (ASIC2b, does not respond to low

pH, ASIC4 is inactive by itself and hence is not thought to encode a proton-gated ion channel), and members have been proposed to function in a wide variety of disease states e.g. pain sensation, ischemia, epilepsy, neurodegenerative diseases, but their role in the brain in is obscure, see Berdiev et al, Ref U, page 15023, second column. The function of these channels in the glia remains a mystery, see Berdiev et al, Ref U, page 15023. Further it has been shown that constitutive amiloride-sensitive currents are a specific feature of the more aggressive brain tumors (see Berdiev et al, Ref U page 15034, column 1). Further, amiloride sensitivity can not be used to infer a specific or well established utility. Berdiev et al, Ref U, discloses the difficulty of assigning a function based on amiloride sensitivity. Berdiev, states (Ref U, page 15034, column 1, second paragraph), "amiloride-sensitive sodium channels cannot easily be classified based on simple biophysical parameters, such as single channel conductance and/or sensitivity to amiloride. This class of ion channel, both in the brain and in epithelial tissues, appear to have a variable composition, and hence tissue-specific differences in biophysical parameters may result from different channel compositions in different tissues". Further the specification provides no significance of the function of amiloride (a drug that blocks sodium/proton antiport and has been used clinically as a potassium sparing diuretic) as it correlates to it role in pain sensation.

The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the ion channel of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to

other known proteins. After further research, a specific and substantial utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicants claimed invention is incomplete. In light of the specification the skilled artisan can conclude that protein of instant invention is a cationic channel protein. However, no disclosure is provided within the instant specification on what specific function the claimed cationic channel protein possesses, nor are any disease states disclosed that are directly related to cation channel dysfunction. Ions are known to play a role of first or second messenger in numerous cellular signaling contexts, but it is not known what role claimed cationic channel plays in signaling and what would be the use of interfering with its function, apart from as targets for drug discovery. Further it is not clear from the specification if the partial channel protein disclosed by the amino acid sequence of SEQ ID NO:4 encoded by SEQ ID NO:3 is functional. The channel protein of SEQ ID NO:4 is considered by Examiner to lack functionality, absent evidence to the contrary. There is no disclosure in the specification which shows the protein of SEQ ID NO:4 was assayed for activity.

The utilities asserted by Applicant are not specific or substantial. Since no specific function of claimed cation channel is known, and the ability to transport ions with no associated function is not considered a "well established utility" the hypothesized functions are based entirely on conjecture from homologous polypeptides, the asserted utilities are not specific to instant polypeptide, but rather are based on family attributes. Neither the specification nor the art of record disclose the nucleic acid

of SEQ ID NO:1, 3 or 8 encoding the protein of SEQ ID NO:2, 4 or 8 or fragments thereof useful to identify drugs that affect said protein and modulate its activity. Similarly, neither the specification nor the art of record disclose any instances where disorders can be affected by interfering with the activity of claimed cation channel. Thus the corresponding asserted utilities are essentially methods of using claimed cation channel to identify or treat disease states associated with cation channel polypeptide dysfunction and as targets for drug discovery. Therefor the asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating or testing for compounds that interact with claimed cation channel, which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed cation channel, further experimentation is necessary to attribute a utility to the claimed cation channel. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the

intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The DNA of the instant invention and the protein encoded thereby are compounds which share some structural similarity to other ion channel proteins based on sequence similarity. The family of proteins related to instant invention may have diverse effects and bind a diverse number of ligands (e.g. syntax in 1A, see Berdiev et al). Although the family of ASIC proteins domains may share some common structural motifs, various members of the family may have different sites of action and different biological effects. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotides/polypeptides. Also, the specification does not predict whether the claimed polynucleotides/polypeptides would be over expressed or under expressed in a specific, diseased tissue compared to the healthy tissue control. The specification contains assertions that the claimed polynucleotides/polypeptides can be used the art

for drug development. However, without a disclosure of a particular disease state in which the claimed polynucleotides/polypeptides are expressed at an altered level or form, it would be impossible to determine what the results of a gene expression/protein expression monitoring assay mean. For example, if a compound is tested on a microarray comprising the claimed polynucleotides and affects expression of the polynucleotides negatively, it cannot be determined if that means that the compound is a potential good drug for a disease or would acerbate the disease if administered. The test results also would not have meaning in terms of what specific disease is relevant. Further, before the claimed invention can have utility in gene expression, significant, further research would have to be conducted to determine which diseases correlate with altered forms or levels of the claimed polynucleotides, and whether the claimed polynucleotides are over expressed or under expressed in the diseased tissue. The disease state itself has to be identified.

The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids/polypeptides. Even if the expression of Applicants individual polynucleotides/polypeptides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

If a molecule is to be used as a surrogate for a disease state (e.g. gene therapy), some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as diagnostics/treatment for diseases. However, in the absence of any disclosed relationship between the claimed polynucleotides or the proteins that are encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, the use of ASIC gene in gene therapy would only serve as the basis for further research. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

The ASCI family is functionally highly diverse. When there is great functional diversity in a structurally related class of compounds, the class cannot be used to predict a utility for a new compound that fits in the class by structural similarity. Such is the case here. The specification has not disclosed a specific disease or disorder of any type wherein the claimed polynucleotides are expressed at altered amounts or forms

relative to the required control healthy tissue. Significant further research would be required of the skilled artisan to identify such a disease or disorder. Therefore the asserted utility is not substantial. The polypeptide encoded by the polynucleotide belongs to a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family.

To employ a protein/nucleic acids of the instant invention in any of the disclosed methods would clearly be using it as the object of further research. Such a use has been determined by the courts to be a utility which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for proteins of SEQ ID NO:2, 4 or 8, then the claimed invention as disclosed does not meet the requirements of 35 U.S.C. §101 as being useful.

5. Applicants argue that as a result of the claim amendment and in light of the arguments set forth above the rejections under 35 U.S.C. 112, first paragraph are obviated. Applicant argues amended claims include sequence identifiers as well as percentage limitation of homology for the functionality equivalent derivatives. As a

result the specification provides a written description of the amended claims. Applicant's arguments have been fully considered but not found persuasive. Applicant's arguments are addressed in the rejections below. The rejections under 35 U.S.C. 112, first paragraph have been recast in view of the amended claims. Claims 1, 11-13, 15, 17-23, and 26-29 rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed cation channel, further experimentation is necessary to attribute a utility to the claimed polypeptides, polynucleotides and methods of their use. The rejection is essential the same as in paper number 23 (2/11/03), but is recast to address the claims as amended. While the person of ordinary skill in the art would, in light of the specification be able to isolate polypeptides represented by SEQ ID NOS: 2, 4 and 8 encoded by the nucleic acid of SEQ ID NOs:1, 3 and 7, respectively, the scope of the claims, which encompass polypeptides and polynucleotides which are functionally equivalent derivative having at least 67% homology to SEQ ID No:2, 4, or 8, which encompasses, mutants, variants, analogs, homologs or derivatives of SEQ ID NOS:2, 4 and 8 are not enabled by the disclosure. There is no disclosure of the function associated with the equivalent derivatives. The specification does not provide a clear definition of the term "functionally equivalent derivative". The specification, on page 2, lines 21-24 discloses,

"The MDEG channel is a structural relative of ASIC channel, the amino acid sequence of which exhibits about 67% homology with the ionic channel MDEG. However, the electrophysiological properties of these two channels are different because they are not activated by the same pH changes". Therefore, based on the specification there is no disclosure of the equivalent function encompassed by the derivatives of at lest 67% homology to SEQ ID NO:2, 4, or 8. On the contrary to Applicants arguments the functions disclosed are not equivalent. The functionally equivalent derivatives encompass polypeptides and polypeptides variants which, although being classified as sensitive to amiloride and activated by protons, may be completely unrelated in their physiological function, or even be inactive (e.g. ASIC4 is inactive by itself, Berdiev et al, page 15023, second column). The specification does not disclose how to use said unrelated if functionally inactive variants. The disclosure does not teach how to make functional mutants, variants, analogs, homologs or derivatives of SEQ ID NOS:2, 4 and 8, or to use a commensurate number of the inactive fragments, mutants, variants, analogs, homologs or derivatives which may be structurally and functionally different to the disclosed proteins of SEQ ID NOs:2, 4 and 8. There is no disclosure of the critical structural feature of the invention or how it relates structure to function. Due to the large quantity of experimentation necessary to identify the polypeptides and polynucleotides of instant invention, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said polypeptides, the unpredictability of the effects of mutation on the structure and function of proteins (since mutations of SEQ ID NO:2, 4 and 8 are also encompassed by the

claims), and the breadth of the claim which fail to recite specific functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope. Further since the compounds of SEQ D NOs 1-4 and 7-8 and their derivatives are not enabled for the reasons given above, methods of using said compounds is also not enabled.

6. Amended claims 1, 11, 17, 18-23 and 26-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing. The claims are directed to isolated and purified protein (SEQ ID NO:2, 4, 8) constituting a mammalian neuronal cationic ASIC channel that is sensitive to amiloride and activated by protons or functionally equivalent derivatives thereof having at least 67% homology to SEQ ID NO:2, 4 or 8. Claims are also drawn to nucleic acid encoding said protein, vectors comprising said nucleic acid, cell comprising said vector, and methods of their use.

The specification discloses the polypeptide of SEQ ID NO:2, 4 and 8 encoded by the polynucleotide of SEQ ID NO:s 1, 3 and 7. Further it is not clear from the specification if the partial channel protein disclosed by the amino acid sequence of SEQ ID NO:4 encoded by SEQ ID NO:3 is functional. The channel protein of SEQ ID NO:4 is

considered by Examiner to lack functionality, absent evidence to the contrary. There is no disclosure in the specification which shows the protein of SEQ ID NO:4 was assayed for activity. The instant disclosure of three distinct polypeptide does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length, truncated, fusion molecules and variants thereof; the The claims encompass polypeptides and polynucleotides which are functionally equivalent derivative having at least 67% homology to SEQ ID No:2, 4, or 8, which encompasses, mutants, variants, analogs, homologs or derivatives of SEQ ID NOS:2, 4 and 8. There is no disclosure of the function associated with the equivalent derivatives. The specification does not provide a clear definition of the term "functionally equivalent derivative". The specification, on page 2, lines 21-24 discloses, "The MDEG channel is a structural relative of ASIC channel, the amino acid sequence of which exhibits about 67% homology with the ionic channel MDEG. However, the electrophysiological properties of these two channels are different because they are not activated by the same pH changes". Therefore, based on the specification there is no disclosure of the equivalent function encompassed by the derivatives of at lest 67% homology to SEQ ID NO:2, 4, or 8. What is functional equivalent derivative of the protein of SEQ ID NO:4, which has no assayed function. On the contrary to Applicants arguments the functions disclosed are not equivalent. The functionally equivalent derivatives encompass polypeptides and polypeptides variants which, although being classified as sensitive to amiloride and activated by protons, may be completely unrelated in their physiological

function, or even be inactive (e.g. ASIC4 is inactive by itself, Berdiev et al, page 15023, second column).

A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by an amino acid sequence, falling within the scope of the genus or of a recitation of structural and functional features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of the claimed genus of polypeptides and polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. The fusion polypeptides, fragments and variants encompassed by the claims do not disclose the critical technical feature of the claimed invention or its relationship to function. For example, polypeptides comprising a fragment or variants of SEQ ID NO:2, 4 and 8 may be completely unrelated to the disclosed polypeptide of SEQ ID NO: 2, 4 and 8, having a different function or even be inactive. The critical technical feature encompassed by the fragments and variants must relate to the encompassed polypeptide, structurally and functionally to the disclosed proteins of SEQ ID NO:2, 4 and 8. The same argument applies to the mutants, variants, analogs, homologs, derivatives and fusion products encompassed by the claims. It is not clear what critical technical feature undisclosed amino acids, disclosed amino acids in a specific fragment, or recited descriptive language provide so as to show a written

description of the invention in full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing. There is no description, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the encoded polypeptides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

The specification further fails to identify and describe the regulatory regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the full length, truncated, fusion products and variants thereof. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus may be highly variant, the disclosure is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

An adequate written description of a protein or nucleic acid molecule requires a precise definition, such as by structure, formula, chemical name, and physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

Accordingly, an adequate written description of a polypeptide is more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the polynucleotide or the encoded protein itself. Accordingly, the specification does not provide a written description of the invention of claims 1, 11, 17, 18-23 and 26-29.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe, enable and use the genus as broadly claimed. The skilled artisan cannot envision the detailed chemical structure of the encompassed proteins and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. It is acknowledged that the skill of the artisan in the molecular biology art is high. However, in the current instance, **there is no clear evidence of activity possessed by the claimed genus of polypeptides that are functionally equivalent derivatives, the critical special technical feature of the polypeptides or how the critical special technical feature encompassed by the genus claimed relates to function.** Because of the lack of guidance in the prior art and current application, one skilled in the art could not predict if the variants of the polypeptide of SEQ ID NO:2, 4 and 8 have the same activity as the protein of SEQ ID NO:2, 4 and 8, since no functional equivalent activity is disclosed, nor the fragments disclosed with the critical special technical feature of the invention. The breadth of the claim come from encompassing

polynucleotide encoding a protein, the fragments or variants which do not have an associated structure which defines the critical special technical feature of the invention. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115). Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid or polypeptide is itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition,

such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

With the exception of SEQ ID NO:2, 4 and 8, the skilled artisan cannot envision the detailed chemical structure of the claimed polypeptide and polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not achieved. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGFs were found unpatentable due to lack of written description for the broad class.

Therefore, only the polypeptide comprising SEQ ID NO:2, 4 and 8, the nucleic acid comprising SEQ ID NOs: 1, 3 and 7, vectors containing said nucleic acid, cells containing said vector and methods using said polypeptide, nucleic acid, vector, cell but not the full breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115). Methods for using derivatives, mutants and variants of SEQ ID NOs:1-4 and 7-8 also do not meet written description for the reasons given above.

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 703-308-9435. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

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Nirmal S. Basi
Art Unit 1646
November 11, 2003.

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600